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(54) Title: TREATMENT OF CARDIAC ABNORMALITIES WITH ARYLOXY PROPANOLAMINES

(57) Abstract: Disclosed is a method of treating cardiac dysfunction cardiac abnormalities with aryloxy propanolamines in a subject in need of such treatment. The method comprises the step of administering to the subject an effective amount of a compound of formula I or VIII.

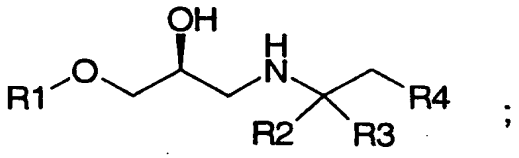
TREATMENT OF CARDIAC ABNORMALITIES WITH ARYLOXY PROPANOLAMINES

BACKGROUND OF THE INVENTION

In recent years many new medications have been developed to treat and/or prevent cardiovascular disease. However, cardiovascular disease often develops as a comorbidity associated with other chronic diseases, for example, obesity and Type II diabetes. The medications which are currently available for treating or preventing cardiovascular diseases, including cardiac dysfunctions, are generally ineffective against obesity and Type II diabetes. It would be advantageous to develop effective therapies for cardiovascular disease which can simultaneously be used to treat other chronic diseases which occur together with cardiovascular disease.

BRIEF SUMMARY OF THE INVENTION

The present invention relates to a method for treating a cardiac abnormality which comprises administering to a subject in need thereof an effective amount of a compound of formula I:



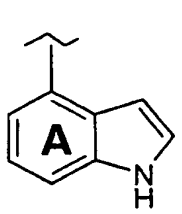
;

I;

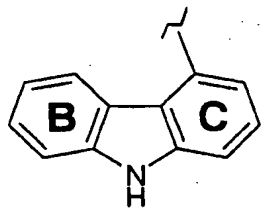
or a physiologically acceptable salt thereof, wherein:

Z is a covalent bond, $-CH_2-$ or $-CH(CH_3)-$;

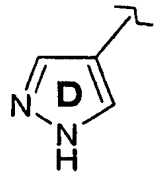
R1 is a moiety of the formula II, III, IV, V or VI:



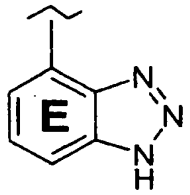
II



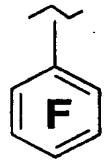
III



IV



V



VI

R2 and R3 are independently -H or C1-C4 alkyl;

R4 is optionally substituted phenyl provided that when R1 is a substituted moiety of formula VI, then R4 is substituted;

Ring **A** through Ring **E** are independently optionally substituted one or more times independently with a moiety selected from the group consisting of: halo, hydroxy, C1-C4 alkyl, C1-C4 haloalkyl, aryl, -CN, -COOR10, -CONHR10, -CONR10R10, -NHCOR10, -OR10, -NHR10, -SR10, $-SO_2R10$, $-SO_2NHR10$ or -SOR10;

Ring **F** is substituted with a group selected from halo, C1-C4 alkyl, hydroxyl, $-SO_2NHR5$, $-CO_2R5$, -CONHR5, $-CF_3$, $-CF_2H$, -NHCOR5 and NH(optionally substituted aryl);

R5 and R6 are independently hydrogen, C1-C4 alkyl or aryl;

R7 and R8 are independently hydrogen, C_1-C_4 alkyl, aryl, $(CH_2)_n$aryl, or R7 and R8 combine with the nitrogen to which each is bound to form morpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl;

R9 is C_1-C_4 alkyl, C_1-C_4 haloalkyl, $(CH_2)_nC_3$-C_8 optionally substituted cycloalkyl, $(CH_2)_n$ optionally

substituted aryl or $(CH_2)_n$ optionally substituted heteroaryl;

R10 is independently hydrogen, C1-C4 alkyl or aryl; and

n is 0, 1 or 2.

Moreover, the present invention relates to a method for modulating the activity of a beta adrenergic receptor, wherein the beta adrenergic receptor is not the beta 1 receptor, the beta 2 receptor or the beta 3 receptor, which comprises administering to a subject in need thereof an effective amount of a compound of formula I.

In addition, the present invention relates to the use of a compound of formula I, or a physiologically acceptable salt thereof, for the preparation of a medicament for treating a cardiac abnormality or for modulating the activity of a beta adrenergic receptor, wherein the beta adrenergic receptor is not the beta 1 receptor, the beta 2 receptor or the beta 3 receptor.

The present invention further relates to a pharmaceutical composition containing a compound of formula I, or a physiological salt thereof, for modulating the activity of a beta adrenergic receptor, wherein the beta adrenergic receptor is not the beta 1 receptor, the beta 2 receptor or the beta 3 receptor.

DETAILED DESCRIPTION OF THE INVENTION

A "subject" is a mammal, preferably a human, in need of treatment (therapeutic or prophylactic) for cardiac dysfunction. In one aspect, the subject is also in need of treatment for obesity and/or Type II diabetes. A "subject" can also be an animal in need of such treatment, e.g., domestic animals (e.g., dogs, cats, and the like), farm animals (e.g., cows, sheep, pigs, horses, and the like) and laboratory animals (e.g., rats, mice, guinea pigs, and the like).

An "effective amount" of a compound is a quantity sufficient to achieve a desired therapeutic and/or prophylactic effect. The amount of compound administered to the individual will depend on the type and severity of the disease and on the characteristics of the individual, such as general health, age, sex, body weight and tolerance to drugs. It will also depend on the degree, severity and type of disease. The skilled artisan will be able to determine appropriate dosages depending on these and other factors. Typically, an effective amount of the compound can range from about 0.05 mg/kg to about 20 mg/kg of the active compound of this invention. Preferred daily doses will be about 0.1 to about 10 mg/kg, more preferably from about 0.1 to about 5 mg/kg.

The term "aryl" includes carbocyclic aromatic groups such as phenyl, 1-naphthyl, 2-naphthyl, 1-anthracyl and 2-anthacyl.

The term "heteroaryl" includes monocyclic rings such as *N*-imidazolyl, 2-imidazole, 2-thienyl, 3-thienyl, 2-furanyl, 3-furanyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidy, 4-pyrimidyl, 2-pyranyl, 3-pyranyl, 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl, 2-pyrazinyl, 2-thiazole, 4-thiazole, 5-thiazole, 2-oxazolyl, 4-oxazolyl and 5-oxazolyl. Heteroaryl groups also include fused polycyclic aromatic ring systems in which a carbocyclic aromatic ring or heteroaryl ring is fused to one or more other heteroaryl rings. Examples include 2-benzothienyl, 3-benzothienyl, 2-benzofuranyl, 3-benzofuranyl, 2-indolyl, 3-indolyl, 2-quinolinyl, 3-quinolinyl, 2-benzothiazole, 2-benzooxazole, 2-benzimidazole, 2-quinolinyl, 3-quinolinyl, 1-isoquinolinyl, 3-quinolinyl, 1-isoindolyl, 3-isoindolyl, and acridintyl.

Also included within the scope of the term "aryl" or "heteroaryl" is a group in which one or more carbocyclic aromatic rings and/or heteroaromatic rings are fused to a

cycloalkyl or non-aromatic heterocyclic ring. Examples include decalin, phthalimido, benzodiazepines, benzooxazepines and benzooxazines and phenothiazines.

The terms "substituted phenyl" and "substituted cycloalkyl" refer to a phenyl or cycloalkyl group that is substituted one or more times independently with a moiety selected from the group consisting of halo, -CN, C_1-C_4 alkyl, C_1-C_4 haloalkyl, -OR9, -CO_2R6, -CONR7R8, -CONH(C1-C4 alkyl), -SR6, -CSNHR6, -CSNR7R8, -SO_2R6, -SO_2NR7R8, -SOR6, -NR7R8, optionally substituted aryl, optionally substituted heteroaryl, or C2-C4 alkenyl substituted with -CN, -CO_2R2 or -CONR7R8.

The terms "substituted aryl" and "heteroaryl" refer to an aryl or heteroaryl group that is substituted one or more times independently with a moiety selected from the group consisting of halo, -CN, C_1-C_4 alkyl, C_1-C_4 haloalkyl, -OR9, -CO_2R6, -CONR7R8, -CONH(C1-C4 alkyl), -SR6, -CSNHR6, -CSNR7R8, -SO_2R6, -SO_2NR7R8, -SOR6, -NR7R8, or C2-C4 alkenyl substituted with -CN, -CO_2R2 or -CONR7R8.

It has now been found that certain beta 3 agonists, specifically certain aryloxy propanolamines, modulate tachycardia. Some of these aryloxy propanolamines are partial agonists/antagonists of tachycardia and cause minimal increases in heart rate while blocking the effects of more potent activators of tachycardia such as isoproterenol and CGP 12177 (see Example 2). For example, the maximal tachycardia exhibited by rat atria in the presence of Compound **2** is only about 15% of the maximal increase in heart rate observed with isoproterenol (Example 2). Other aryloxy propanolamines, e.g., Compounds **1** and **8**, are antagonists of tachycardia (Example 2). The structures of these aryloxy propanolamines are shown below. Based on these discoveries, improved methods of treating cardiac abnormalities are disclosed.

The invention disclosed herein is directed to a method of treating cardiac abnormalities in a subject. The method comprises administering to the subject an effective amount of a compound represented by Structural Formula (I) or (VIII) to the subject. One advantage of the present method is that the aryloxy propanolamines used in the method are also beta 3 agonists and are therefore also effective in the treatment of obesity and Type II diabetes. Thus, patients can be simultaneously treated for certain cardiac abnormalities and for obesity or Type II diabetes with the disclosed method.

The aryloxy propanolamines disclosed herein can modulate tachycardia in addition to activating the beta 3 receptor. The data disclosed herein is consistent with these compounds acting at a new beta adrenergic receptor, referred to as the "beta 4 receptor", to modulate tachycardia. Specifically, these aryloxypropanolamines modulate tachycardia in the presence of propranolol (Example 2), a beta 1 and beta 2 receptor antagonist. In addition, cardiostimulation by CGP 12177 is known to occur in both wild type and beta 3 knock-out mice, indicating that the beta 3 receptor plays little or no role in modulating tachycardia (Kaumann *et al., Molecular Pharmacology 53*:670 (1998)). Thus, it is likely that these compounds affect tachycardia by acting at a site other than the beta 1, beta 2 or beta 3 receptor. Based on these results, the present invention is also related to a method for modulating (activating or inhibiting) a beta adrenergic receptor other than beta 1, beta 2 or beta 3 in a subject in need of such modulation by administering to the subject an effective amount of a compound of formula I or VIII.

As discussed above, the aryloxy propanolamines used in the method of the present invention are believed to inhibit a beta adrenergic receptor that is not beta 1, beta 2 or

beta 3, or to cause only mild activation of this beta adrenergic receptor while blocking the effects of more potent activators such as isoproterenol or CGP 12177. Thus, desirable physiological effects that are mediated by blockage of this beta adrenergic receptor can be achieved in a subject by administering an effective amount of an aryloxy propanolamine disclosed herein to the subject. Examples of desirable physiological effects which can be achieved by blockage of this receptor include, but are not limited to, the reduction of abnormally rapid heart beat or of irregularities in heart beat.

The methods of treatment disclosed herein can be used to treat, prevent or slow the onset of certain cardiac abnormalities and/or to alleviate the symptoms of such cardiac abnormalities in subjects. Cardiac abnormalities which can be treated (prophylactically or therapeutically) by the method of the present invention are those which are characterized by, could result in and/or could cause abnormally rapid or irregular heart rate. For example, the method of the present invention can be used to slow abnormally rapid or regulate irregular heart beat. Examples of such cardiac abnormalities include arrhythmias such as atrial and ventricular tachycardia, fibrillation, flutter, and atrioventricular nodal reentry as well as cardiac dysfunctions such as angina and congestive heart failure (systolic and diastolic).

The aryloxy propanolamines used in the method disclosed herein are also effective in treating Type II diabetes and obesity (see, for example, WO 97/10822 to Bell *et al.*, WO 98/09625 to Crowell *et al.*, and U.S. Patent No.'s 5,808,080 and 6,046,227, the entire teachings of which are incorporated herein by reference). Thus, the method of the present invention is particularly suited to treating cardiac abnormalities in subjects who: 1) have or are at risk for

developing Type II diabetes; and/or 2) are obese or are at risk for becoming obese. The disclosed method can achieve a number of additional therapeutically or prophylactically beneficial effects in such subjects, including, for example, weight loss, a reduced increase in weight gain compared with untreated subjects and/or decreased insulin tolerance or a reduced increase in insulin tolerance compared with untreated subjects.

Certain compounds of the invention are particularly interesting and are preferred for the uses, methods and formulations describe herein. The following listing sets out several groups of preferred compounds. It will be understood that each of the listings may be combined with other listings to create additional groups of preferred compounds.

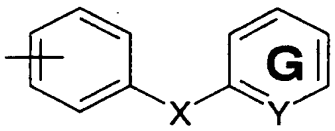
Z is a covalent bond.

R1 is the substituted indolyl group of formula II or the substituted carbazolyl group of formula III.

R2 and R3 are both methyl.

R4 is a phenyl group substituted with one or more substituents.

R4 is a moiety of the formula VII:



VII;

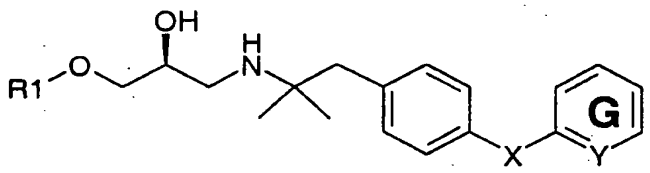
wherein:

ring **G** is unsubstituted or substituted as described above for ring **F**;

X is a covalent bond, $-CH_2-$ -O- or $-NHSO_2-$, preferably -O-; and

Y is -CH- or -N-, preferably, -N-.

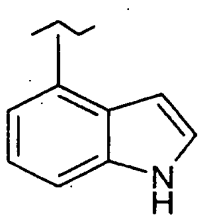
A compound of the formula VIII:



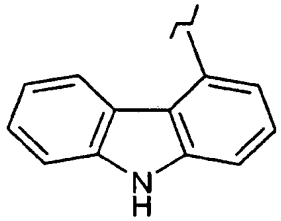
VIII;

wherein:

R1 is a moiety of the formula IX or X:



IX



X

and X, Y and ring **G** are as defined above for the moiety of formula VII, is particularly preferred for the uses, methods and formulations described herein.

An even more preferred compound of formula VIII is one where ring **G** is substituted with -CN or $-CONH_2$. Most preferred is a compound of formula VIII wherein R1 is a moiety of formula IX and ring **G** is substituted with $-CONH_2$.

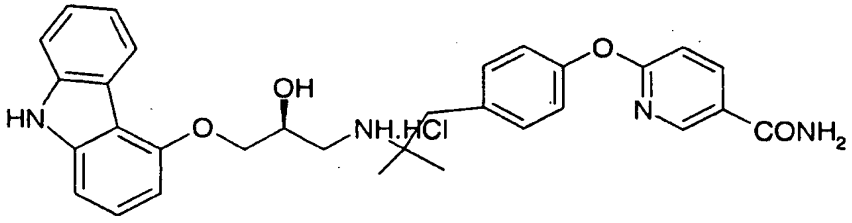
Also included in the present invention are physiologically acceptable salts of the compounds of formula I and VIII. Salts of compounds containing an amine or other basic group can be obtained, for example, by reacting with a suitable organic or inorganic acid, such as hydrogen chloride, hydrogen bromide, acetic acid, perchloric acid, para-toluenesulfonic, methanesulfonic, oxalic, para-bromophenylsulfonic, carbonic, succinic, citric, benzoic, acetic acid and the like. Compounds with a quaternary ammonium group also contain a counteranion such as chloride, bromide, iodide, acetate, sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, mono-hydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate,

propionate, decanoate, caprylate, acrylate, formate, isobutyrate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, 2-butyne-1,4 dioate, 3-hexyne-2, 5-dioate, benzoate, chlorobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, hippurate, β-hydroxybutyrate, glycolate, maleate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate and the like salts.

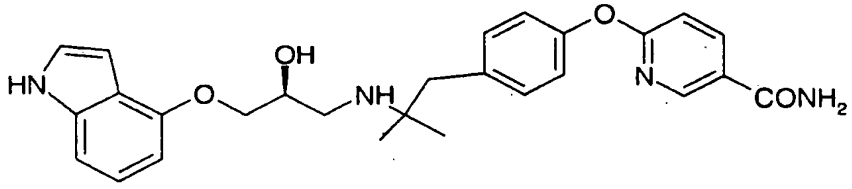
Salts of compounds containing a carboxylic acid or other acidic functional group can be prepared by reacting with a suitable base, for example, a hydroxide base or amine. Salts of acidic functional groups contain a countercation such as ammonium, sodium, potassium and the like.

The following compounds are exemplary aryloxy propanolamines which can be used in the present invention and reference numbers corresponding thereto.

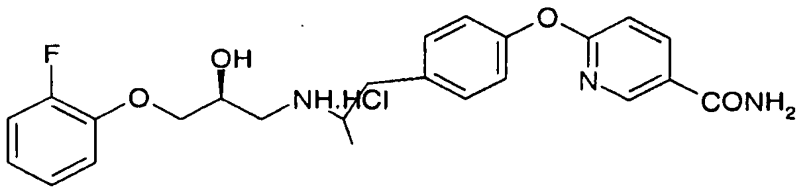
Compound **1**



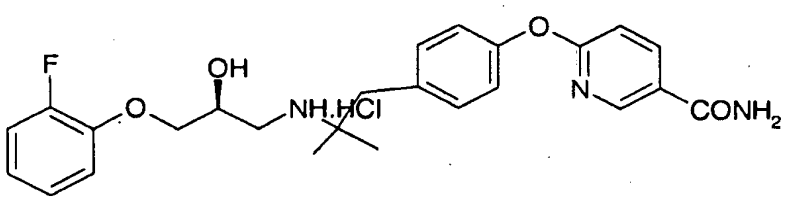
Compound **2**



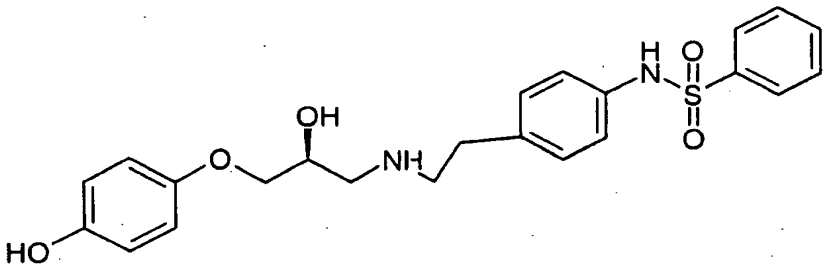
Compound **3**



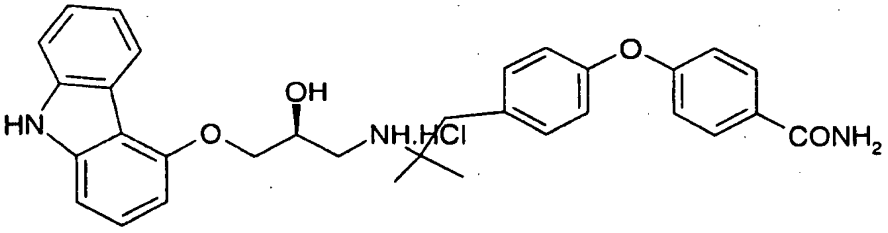
Compound **4**



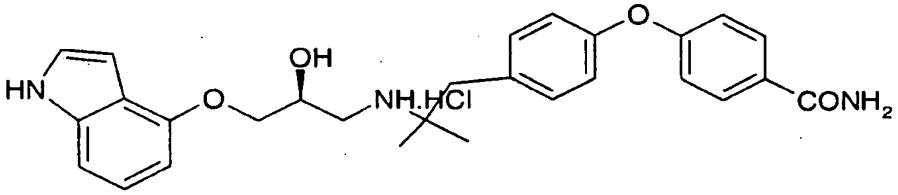
Compound **5**



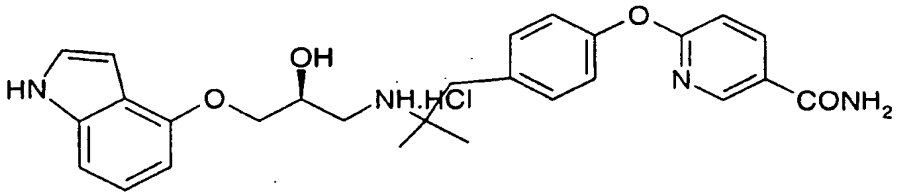
Compound **6**



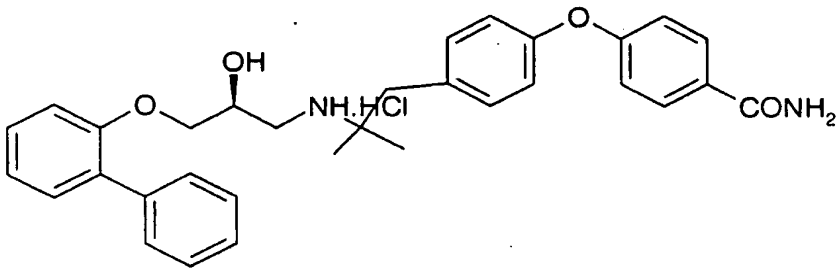
Compound **7**



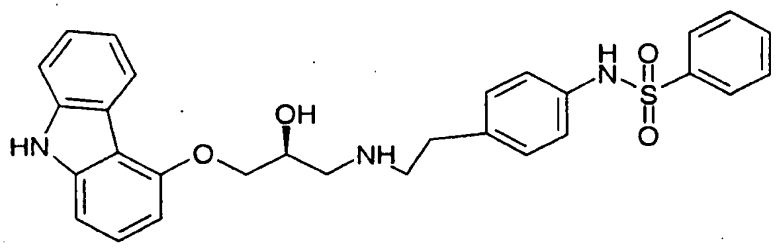
Compound **8**



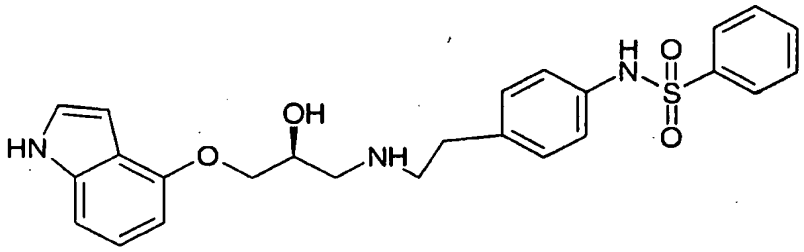
Compound **9**



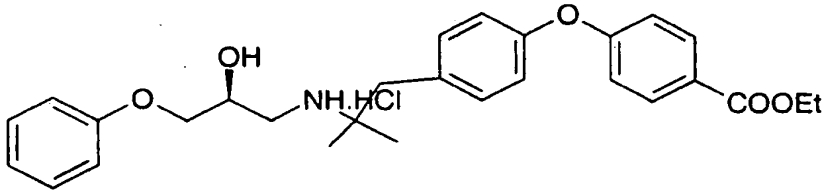
Compound **10**



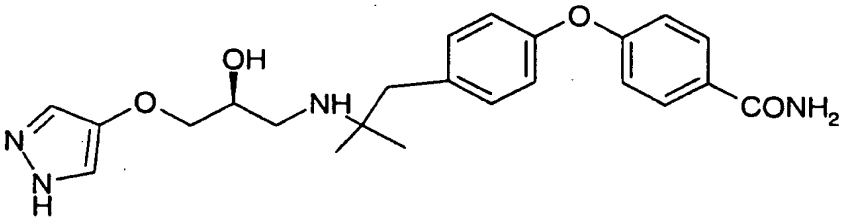
Compound **11**



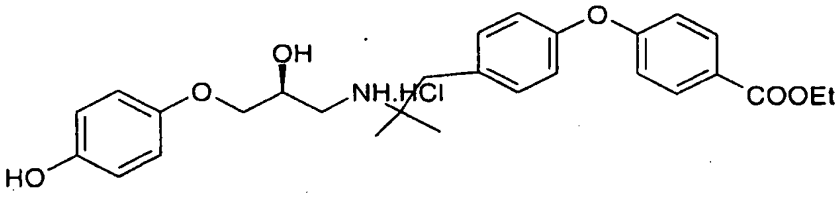
Compound **12**



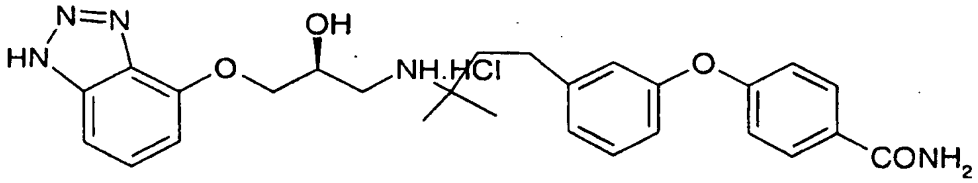
Compound **13**



Compound **14**



Compound **15**



The aryloxy propanolamines used in the present invention can be administered by any suitable route, including, for example, orally in capsules, suspensions or tablets or by parenteral administration. Parenteral administration can include, for example, systemic administration, such as by intramuscular, intravenous, subcutaneous, or intraperitoneal injection. The compound can also be administered orally (e.g., dietary), topically, by inhalation (e.g., intrabronchial, intranasal, oral inhalation or intranasal drops), or rectally, depending on the disease or condition to be treated. Oral is a preferred mode of administration.

The aryloxy propanolamines used in the present invention can be administered to the individual in conjunction with an acceptable pharmaceutical carrier as part of a pharmaceutical composition for treatment of obesity or Type II diabetes. Formulation of an aryloxy propanolamine to be administered will vary according to the route of administration selected (e.g., solution, emulsion, capsule). Suitable pharmaceutical carriers may contain inert ingredients which do not interact with the compound. Standard pharmaceutical formulation techniques can be employed, such as those described in Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, PA. Suitable pharmaceutical carriers for parenteral administration include, for example, sterile water, physiological saline, bacteriostatic saline (saline containing about 0.9% mg/ml benzyl alcohol), phosphate-buffered saline, Hank's solution, Ringer's-lactate and the like. Methods for encapsulating compositions (such as in a coating of hard gelatin or cyclodextran) are known in the art (Baker, *et al.*, "Controlled Release of Biological Active Agents", John Wiley and Sons, 1986).

The aryloxypropanolamines used in present invention can be prepared according to procedures disclosed in WO 97/10822

to Bell *et al.*, WO 98/09625 to Crowell *et al.*, and U.S. Patent No.'s 5,808,080 and 6,046,227, the entire teachings of which are incorporated herein by reference.

The invention is illustrated by the following examples which are not intended to be limiting in any way.

EXEMPLIFICATION

Example 1 - Determination of EC_{50} Values for Aryloxy Propanolamines at the Human Beta 3 Receptor

The two exon human β3 adrenergic receptor was subcloned into the BClI restriction site using a phd expression vector before transfection into the DXB-11, Chinese hamster ovary (CHO) cell line by calcium phosphate precipitation methodology. Additional details are provided in Granneman *et al., Molecular Pharmacology 44:*264 (1993) and Grinnell *et al. Bio/Technology 5:*1189 (1987) the entire teachings of which are incorporated herein by reference. The stably transfected cells were grown to 95% confluency in 95% Dulbecco's modified Eagles Medium (DMEM), 5% fetal bovine serum, 0.01% proline. Media was removed and the cells were washed with phosphate buffered (pH 7.4) saline (without magnesium and calcium). Cells were then lifted using an enzyme free cell dissociation solution (Specialty Media, Lavallette, New Jersey) and pelleted by centrifugation. The cells were resuspended and added (15,000/well) to a 96-well plate. Cells were incubated at 37°C with test compounds for 20 minutes in buffer (Hank's balanced salt solution, 10 mM HEPES, 0.1% BSA, 1 mM L-ascorbic acid, 0.2% dimethyl sulfoxide, 1 mM 3-isobutyl-1-methylxanthine, pH 7.4). After halting the incubation with quench buffer (50 mM Na Acetate, 0.25% Triton X-100, pH 5.8), the c-AMP level was quantified by scintillation proximity assay (SPA) using a modification of the commercially available c-AMP kit (Amersham, Arlington

Heights, IL) with rabbit anti-cAMP antibody (ICN Biomedicals, Aurora, Ohio).

The EC_{50} was assessed as the concentration producing 50% of the maximum response to each test compound. The percent maximal response for each test compound was assessed relative to the maximal response to isoproterenol by dividing the maximal response to the test compound by the maximal response to isoproterenol x 100. The results for each compound tested are shown in Tables 1 and 2.

Example 2 - Determination of EC_{50} values and K_B Values of Aryloxy Propanolamines for Tachycardia

Male rats (approximately 300 grams) (Harlan Industries, Inc., Cumberland, Indiana, USA) were killed by cervical dislocation. Hearts were removed and the left and right atria were dissected and mounted with thread in tissue baths containing 10 mls of modified Krebs' solution. An initial optimum resting force of 1 gram was applied to the atria according to procedures described in Cohen *et al., Naunyn-Schmied Arch. Pharmacol. 320:*145 (1982), the entire teachings of which are incorporated herein by reference. Tissues were allowed to equilibrate approximately 30 minutes in the presence of 3×10^{-7} M propranolol with vigorous oxygenation before exposure to drugs.

To evaluate the ability of test compounds to increase heart rate, test compounds were added cumulatively once the spontaneous atrial rate reached a steady state from the previous addition. Agonist addition was continued until no further increase in atrial rate occurred or until a concentration of 10^{-4} M was reached. The increase in beats per minute (BPM) from baseline heart rate prior to agonist administration was measured for each concentration of agonist by means of a Beckmann Cardiotachometer or a

computerized data acquisition system (BioPac Systems, Inc., Santa Barbara, CA).

The EC_{50} was assessed as the concentration producing 50% of the maximum response to each agonist. The results for each compound tested are shown in Table 1.

Table 1

	Human Beta-3		Rat Tachycardia	
Compound	%*	EC_{50} nM	E_{max}+	EC_{50} nM
1	74 ± 1	< 4	0.0	---
2	68 ± 1	7 ± 0.5	16.3	78.0
3	---	---	21.5	245.0
4	34 ± 1	18 ± 5	14.0	282.0
5	66 ± 3	8 ± 1	0.0	---
6	54 ± 3	8 ± 1	18.0	120.0
7	57 ± 3	11 ± 2	0.0	---
9	20 ± 3	20 ± 5	0.0	---
10	24 ± 3	16 ± 4	0.0	---
11	51 ± 3	47 ± 9	0.0	---
12	---	---	5.3	3100
13	70 ± 35	86 ± 8	25.0	880.0
14	78 ± 4	497 ± 126	20.6	2530
15	48 ± 3	24 ± 2	27.3	270

* Percent maximal response relative to isoproterenol (100%)

+ Maximal tachycardia in beats/minute

As can be seen from Table 1, Compounds **2-4**, **6** and **12-15** are mixed agonists/antagonists of tachycardia in rat atria, but provide less than 25% of the maximum activation caused by isoproterenol. Table 1 also shows, based on EC_{50} values, that the concentrations required to affect tachycardia are generally at least about ten fold higher than the concentrations required to stimulate the beta 3 receptor.

To evaluate the ability of test compounds to inhibit tachycardia, test compounds were evaluated by preincubation with tissue for approximately 20-30 minutes. Cumulative concentration responses to CGP 12177 were determined in the presence of test compound or vehicle. Antagonist equilibrium dissociation constants K_B were determined according to the following equation:

$$K_B = \frac{[B]}{[DR - 1]}$$

where [B] is the concentration of the test compound and dose ratio (DR) is the EC_{50} value of CGP 12177 in the presence of the test compound divided by the control EC_{50} value of CGP 12172. The K_B values are shown in Table 2 along with the human beta 3 EC_{50} values for comparison.

Table 2

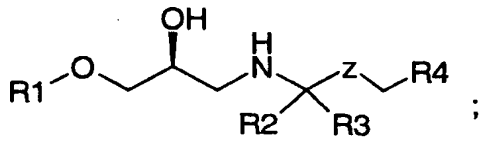
Compound	Human Beta-3 EC_{50}	Rat Tachycardia K_B
1	< 4 nM	48 nM
7	11 ± 2 nM	135 nM
8	---	35 nM
11	47 ± 9	616 nM
12	39.0 nM	1230 nM

The compounds in Table 1 having a rat tachycardia EC_{50} value of 0.0 are possible antagonists of tachycardia. Confirmed antagonists demonstrate the ability to block activation of tachycardia by agonists such as CGP 12177, as described above. Compounds **1**, **7-8** and **11-12** are confirmed antagonists of tachycardia, as shown in Table 2.

CLAIMS

What is claimed is:

1. A method of treating a cardiac abnormality in a subject in need thereof, the method comprising the step of administering to the subject an effective amount of a compound of formula I:



;

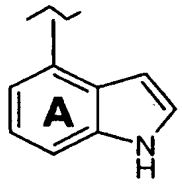
I;

or a physiologically acceptable salt thereof,

wherein:

Z is a covalent bond, $-CH_2-$ or $-CH(CH_3)-$;

R1 is a moiety of the formula II, III, IV, V or VI:



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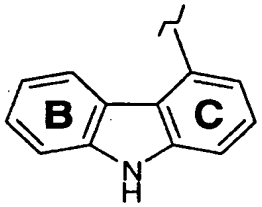

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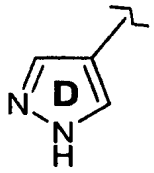

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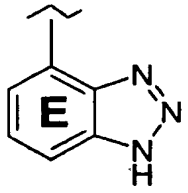


V

VI

R2 and R3 are independently -H or C1-C4 alkyl;

R4 is optionally substituted phenyl provided that when R1 is a substituted moiety of formula VI, then R4 is substituted;

Ring **A** through Ring **E** are independently optionally substituted one or more times independently with a moiety selected from the group consisting of: halo, hydroxy, C1-C4

alkyl, C1-C4 haloalkyl, aryl, -CN, -COOR10, -CONHR10, -CONR10R10, -NHCOR10, -OR10, -NHR10, -SR10, $-SO_2R10$, $-SO_2NHR10$ or -SOR10;

Ring **F** is substituted with a group selected from halo, C1-C4 alkyl, hydroxyl, $-SO_2NHR5$, $-CO_2R5$, -CONHR5, $-CF_3$, $-CF_2H$, -NHCOR5 and NH(optionally substituted aryl);

R5 and R6 are independently hydrogen, C1-C4 alkyl or aryl;

R7 and R8 are independently hydrogen, C_1-C_4 alkyl, aryl, $(CH_2)_n$aryl, or R7 and R8 combine with the nitrogen to which each is bound to form morpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl;

R9 is C_1-C_4 alkyl, C_1-C_4 haloalkyl, $(CH_2)_nC_3$-C_8 optionally substituted cycloalkyl, $(CH_2)_n$ optionally substituted aryl or $(CH_2)_n$ optionally substituted heteroaryl;

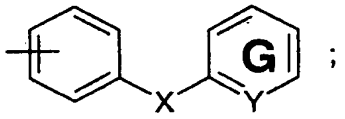
R10 is independently hydrogen, C1-C4 alkyl or aryl; and n is 0, 1 or 2.

2. The method of Claim 1 wherein Z is a covalent bond.

3. The method of Claim 2 wherein the subject is being administered the compound to treat obesity or Type II diabetes.

4. The method of Claim 2 wherein:
R2 and R3 are both methyl; and
R4 is substituted phenyl.

5. The method of Claim 4 wherein R4 is a moiety of formula VII:



;

VII;

wherein:

Ring **G** is substituted or unsubstituted;

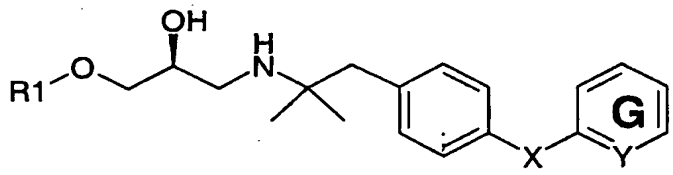
X is a covalent bond, $-CH_2-$ -O- or $-NSO_2-$; and

Y is -CH- or -N-.

6. The method of Claim 5 wherein:

R1 is a substituted moiety of formula II or III.

7. A method of treating a cardiac abnormality which comprises administering to a subject in need thereof an effective amount of a compound of formula VIII:



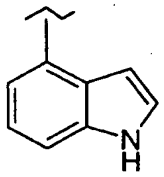
;

VIII;

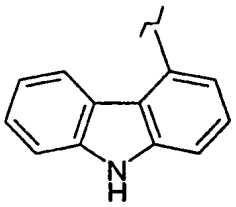
or a physiologically acceptable salt thereof,

wherein:

R1 is a moiety of formula IX or X:



; or



;

IX X;

Ring **G** is substituted or unsubstituted;

X is a covalent bond, $-CH_2-$ -O- or $-NSO_2-$; and

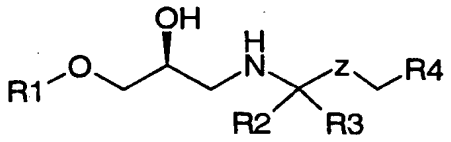
Y is -CH- or -N-.

8. The method of Claim 7 wherein the subject is being administered the compound to treat obesity or Type II diabetes.

9. The method of Claim 8 wherein -X- is -O- and Ring **G** is substituted with $-CONH_2$ or -CN.

10. The method of Claim 10 wherein R1 is a moiety of formula IX, Ring **G** is substituted with -CONH2 and Y is -N-.

11. A method for modulating the activity of a beta adrenergic receptor, wherein the beta adrenergic receptor is not the beta 1 receptor, the beta 2 receptor or the beta 3 receptor, which comprises administering to a subject in need thereof an effective amount of a compound of formula I:



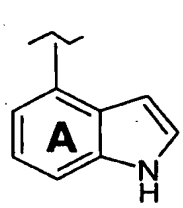
;

or a physiologically acceptable salt thereof,

wherein:

Z is a covalent bond, $-CH_2-$ or $-CH(CH_3)-$;

R1 is a moiety of the formula II, III, IV, V or VI:



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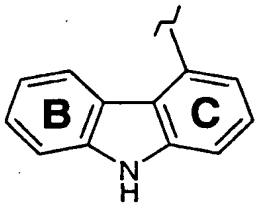

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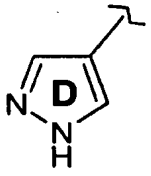
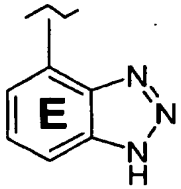


IV



V

VI

R2 and R3 are independently -H or C1-C4 alkyl;

R4 is optionally substituted phenyl provided that when R1 is a substituted moiety of formula VI, then R4 is substituted;

Ring **A** through Ring **E** are independently optionally substituted one or more times independently with a moiety selected from the group consisting of: halo, hydroxy, C1-C4 alkyl, C1-C4 haloalkyl, aryl, -CN, -COOR10, -CONHR10, -CONR10R10, -NHCOR10, -OR10, -NHR10, -SR10, $-SO_2R10$, $-SO_2NHR10$ or -SOR10;

Ring **F** is substituted with a group selected from halo, C1-C4 alkyl, hydroxyl, $-SO_2NHR5$, $-CO_2R5$, -CONHR5, $-CF_3$, $-CF_2H$, -NHCOR5 and NH(optionally substituted aryl);

R5 and R6 are independently hydrogen, C1-C4 alkyl or aryl;

R7 and R8 are independently hydrogen, C_1-C_4 alkyl, aryl, $(CH_2)_n$aryl, or R7 and R8 combine with the nitrogen to which each is bound to form morpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl;

R9 is C_1-C_4 alkyl, C_1-C_4 haloalkyl, $(CH_2)_nC_3$-C_8 optionally substituted cycloalkyl, $(CH_2)_n$ optionally substituted aryl or $(CH_2)_n$ optionally substituted heteroaryl;

R10 is independently hydrogen, C1-C4 alkyl or aryl; and n is 0, 1 or 2.

12. A use of a compound of formula I, as defined in Claim 1, or a physiologically acceptable salt thereof, for the preparation of a medicament for treating a cardiac abnormality or for modulating the activity of a beta adrenergic receptor, wherein the beta adrenergic receptor is not the beta 1 receptor, the beta 2 receptor or the beta 3 receptor.

13. A pharmaceutical composition containing a compound of formula I, or a physiological salt thereof, for modulating the activity of a beta adrenergic receptor, wherein the beta adrenergic receptor is not the beta 1 receptor, the beta 2 receptor or the beta 3 receptor.